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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/776,044	02/26/97	BYWATER M	1614-178P

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EXAMINER	
HOLLERAN, A	
ART UNIT	**PAPER NUMBER**
1642	23

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/776,044	Bywater t al.
Examiner	**Group Art Unit**
Anne Holleran	1642

☒ Responsive to communication(s) filed on *Dec. 7, 2000*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-10, 14, and 15* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-10, 14, and 15* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Continued Prosecution Application

1. The request filed on Dec. 7, 2000 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 08/776,044 is acceptable and a CPA has been established. An action on the CPA follows.

2. Claims 1-10, 14 and 15 are pending.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections Withdrawn:

4. The rejection of claims 1-9, 14 and 15 under 35 U.S.C. 112, first paragraph is withdrawn in view of the amendment removing the reference to the complete coding region of cancer-related p53. The rejection is maintained for claim 10.

Claim Rejections Maintained:

5. The rejection of claim 10 under 35 U.S.C. 112, first paragraph, as containing subject matter that was not disclosed in the original specification, is maintained.

As discussed in previous Office Actions, the specification lacks specific support for a method that comprises amplifying a sequence corresponding to the complete coding region of the p53 gene. A claim to a specific embodiment of a method for prognostication of cancer comprising sequencing the entire coding region of a DNA encoding a p53 protein introduces new matter into the specification because this specific embodiment was not contemplated by the inventors at the time the application was filed.

6. The rejection of 15 under 35 U.S.C. 102(e) as being anticipated by Diamandis et al (U.S. Patent No. 5,552,283; issued Sep. 1996; filed Feb. 1995; continuation in part of U.S. Patent 5,545,527, filed July 8, 1994) is maintained for the reasons of record.

With respect to amended claim 15, Applicant's arguments that the amendment overcomes the art of record have been considered but not found persuasive. Applicant specifically points to the step "b" of claim 15 in which the entire sequence determined in step "b" is analyzed for the presence of mutations. Applicant asserts that as currently recited the claims read on analyzing the entire coding region of a p53 nucleic acid which Applicant asserts is not taught by Diamandis et al. This argument is not found persuasive because the nucleotide sequence determined in step "a" appears to be a nucleotide sequence which encodes a part of a p53 protein. Thus, Applicant is arguing for a limitation that is not present in the claims.

The rejection of claim 15 under 35 U.S.C. 102(e) as being anticipated by Diamandis et al is made again. Diamandis et al teaches that p53 mutations are correlated with more aggressive tumors, metastasis and lower 5 year survival rates (column 1, lines 34-38). Thus, Diamandis et al

teaches that detection of p53 mutations may be used in determining the prognosis of a cancer patient. Diamandis et al teaches a method of detecting p53 mutations by direct sequencing of a part of the genomic DNA encoding a biologically functional domain of a p53 protein (column 14, lines 21 - 51 and column 15, lines 56-63). Diamandis et al teaches detecting mutations in exon 7. Exon 7 is known to contain a DNA binding domain (see Hartmann et al. Trends in Genetics, 13: page 28, 1997; made of record in Office Action mailed June 10, 1998). Thus, Diamandis et al teaches the method of claim 15.

7. The rejection of Claims 1-10 and 14 under 35 U.S.C. 103(a) as being unpatentable over Elledge et al. (Breast Cancer Res. Treat. 27: 95-102, 1993) and of Callahan (J. Natl. Cancer Institute, 84: 826-827, 1992) in view of Diamandis et al (U.S. Patent No. 5,552,283) is maintained for the reasons of record. Applicant presents no arguments why amended claims 1-10 and 14 are not obvious over the art of record.

8. The denial of priority under 35 U.S.C. 119(a-e) is maintained for claim 10.

New Grounds of Rejection:

9. Claims 1-10, 14 and 15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 14 and 15 are vague and indefinite because of the phrase "biologically functional domains". All parts of a protein contribute to the overall function of a protein. Also, is the biological function referring to the function of a p53 protein or to a part of a gene encoding a p53 protein ? For purposes of examination, claims 1, 14 and 15 will be interpreted to be methods comprising a first step of determining the nucleotide sequence of any part of p53 gene.

Claims 1, 14 and 15 are vague and indefinite because the phrase "the parts of a cancer-related ..." lacks antecedent basis. This rejection would be overcome by amending the claim to read "parts of a cancer-related ...".

Claims 1, 14 and 15 are vague and indefinite because they are drawn to methods having a step which is that of determining the nucleotide sequence of a part of p53 protein. A protein does not have a nucleotide sequence.

Claims 1, 14 and 15 are vague and indefinite because step "d" is an inactive step. Because of the word "using" there is no active step. To render step "d" an active step, the step might be amended to read "d) prognosticating the development of the neoplasia by combining the results of steps c) (I) and c (ii).". However, it is not clear what is meant by "combining the results of steps c) (I) and c (ii)". The specification teaches a method wherein patients are divided into 1 of 4 groups depending on whether or not their tumor has a p53 mutation and whether or not the patient is node positive. What is lacking from the claims 1, 14, and 15 is a clear recitation of what step is performed after a patient is assessed for the presence of absence of a p53 mutation and assessed for node status and how the classification results in prognostication of neoplasia.

Claim 1 is further vague and indefinite because the step "d" does not correlate with the preamble which is, in part, directed to a method of obtaining guidance for treatment. Step "d" is directed to "providing" guidance for treatment.

Claims 1, 14 and 15 are vague and indefinite in the recitation "prognostication of the development of neoplasia". Does this phrase indicate that the claimed methods encompass methods of prognosticating the probability that a person without cancer will later develop cancer ? The specification does not provide specific support for the phrase "prognostication of the development of neoplasia" and appears to only describe methods to be used in the prognosis of a patient already diagnosed with cancer.

Claim 2 is vague and indefinite because it is not clear when and how the method includes a step for typeing of a p53 mutation because claim 1 only recites steps involving determining the presence or absence of a p53 mutation. It is also not clear how the typeing of a p53 mutation is to be used as a prognostication factor.

Claim 3 is vague and indefinite because there is no antecedent basis in either claim 1 or in claim 2 for a method comprising determining the position of a mutation and basing a prognostication on the position of the mutation.

Claim 3 is also vague and indefinite because the phrase "the biological aggressiveness and/or metastatic potential of the neoplasia" lacks antecedent basis. This rejection would be overcome if the phrase were amended to delete "the" from the beginning of the phrase. Claim 3 is also vague and indefinite because claim 3 is directed to a method to categorize biological aggressiveness and/or metastatic potential of a neoplasia but depends from claim 2 which is a

method which is directed to prognostication of the development of neoplasia and obtaining guidance for treatment.

Claim 10 is vague and indefinite because it is not clear which method steps are included in the method and which are not. Claim 10 depends from claim 1 and, therefore, should be a method comprising all of the steps of claim 1. However, claim 10 appears to be drawn to a method with different steps from the steps of the method of claim 1.

Claim 10 is vague and indefinite because the phrase "the sequences corresponding to the complete coding region of the p53 gene" lacks antecedent basis. This rejection would be obviated by amending claim 10 to read "a sequence corresponding to the ...".

Claim 10 is also vague and indefinite because it is drawn to an assay method without a correlation step.

10. Claim 3 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 3 is drawn to a method for prognostication of the development of neoplasia and obtaining guidance for treatment comprising analyzing a nucleotide sequence encoding a part of a p53 protein for either a missense mutation, a nonsense mutation, a deletion mutation or an insertion mutation. The presence, position and type of a mutation is used to categorize the biological aggressiveness and/or metastatic potential of the neoplasia. The specification does not

appear to provide specific support for an embodiment of the claimed invention wherein a prognosis is made of the biological aggressiveness and/or metastatic potential of a neoplasia based on a determination of whether a tumor has a p53 mutation and whether a patient is node positive or not.

The specification provides a working example which demonstrates differences in duration of relapse-free survival and death as prognostic endpoints but which does not demonstrate differences in biological aggressiveness and/or metastatic potential as prognostic endpoints. Additionally, the specification does not provide methods and specific examples of how one would devise a specific measure of biological aggressiveness and/or metastatic potential; and how one would categorize biological aggressiveness and/or metastatic potential. No specific categories are described. The specification does provide specific support for methods where the prognostic endpoint is duration of relapse-free survival and death but these endpoints are not the same as the endpoints of biological aggressiveness and/or metastatic potential either in scope or in how one would define a categorization scheme.

11. Claim 3 is rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement commensurate with the scope of the claimed invention. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation would be required for the practice of the full scope of the claimed inventions are: 1) quantity of experimentation

necessary; 2) the amount of direction or guidance presented in the specification; 3) the presence or absence of working examples; 4) the nature of the invention; 5) the state of the prior art; 6) the relative skill of those in the art; 7) the predictability or unpredictability of the art; and 8) the breadth of the claims. See Ex parte Forman, 230 USPQ 546, BPAI, 1986.

Claim 3 is interpreted as described above. Thus, claim 3 is broadly drawn to methods of prognostication of any type of cancer by analyzing the nucleotide sequence encoding p53 protein for mutations.

The specification limits the working examples to an analysis of breast cancer and the prognostication endpoints to relapse-free survival and death. Thus, the scope of claim 3 is broader than the scope of the working examples provided. Because different cancers have different causes and course of disease, a correlation between biological aggressiveness and/or metastasis and p53 mutations for one type of cancer using a specific methodology does not necessarily reasonably enable one of skill in the art to prognosticate biological aggressiveness and/or metastasis in any type of cancer. Dahse et al (Dahse, R. Et al. Int. J. Mol. Med, 4(3): 279-283, 1999; ~~abstract only~~) teaches that in head and neck cancers, that the frequency of p53 mutations did not correlate with tumor stage or tumor site. Lung et al (Lung, M.L. et al. Chest, 109: 718-726, 1996; ~~abstract only~~) teaches that in lung cancer that there is no significant correlation between the detection of p53 aberrations and tumor stage. Thus, the teachings of both Dahse et al and Lung et al provide evidence that finding a correlation between p53 mutation and biological aggressiveness/and or metastasis is not predictable for all cancers.

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Given the broad scope of claim 3, the lack of guidance in the specification as to the exact definition of what is encompassed by biological aggressiveness and/or metastasis, evidence in the art that p53 mutations do not always correlate with various parameters of biological aggressiveness and/or metastasis, one of skill in the art would be required to engage in undue experimentation to practice the claimed invention commensurate with the scope of the claimed invention.

12. Claim 2 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 2 is drawn to a method for prognostication of the development of neoplasia and obtaining guidance for treatment comprising analyzing a nucleotide sequence encoding a part of a p53 protein and typeing the mutation as either a missense mutation, a nonsense mutation, a deletion mutation or an insertion mutation. As described above, it is not clear what role the typeing step plays in the claimed prognostication methods. However, one interpretation is that the subtype of p53 mutation is a prognostication factor and could be used to provide a patient with a prognois of his cancer.

However, the specification does not appear to provide specific support for embodiments of the claimed methods wherein a prognosis is made based on a determination of whether a tumor has a a missense mutation, a nonsense muation, a deletion mutation or an insertion mutation.

The specification provides a working example which demonstrates differences prognosis of patients depending on whether a p53 mutation was detected and whether a patient was node positive or not. The specification also teaches that p53 mutations are not all the same and may be categorized into different subtypes. However, the ability to detect the various subtypes of p53 mutation and to categorize a tumor as having such a mutation type does not confer upon the Applicant possession of a prognostic method wherein a particular type of mutation is correlated with any type of cancer outcome. Thus, one of skill in the art would not find that Applicant was in possession of the invention as claimed at the time the invention was filed.

13. Claim 15 is rejected under 35 U.S.C. 102(b) as being anticipated by Thorlacius et al (Thorlacius, S. et al. Cancer Res. 53: 1637-1641, 1993; cited in the IDS).

Claim 15 is drawn to a method of prognosticating neoplasia in a human patient having neoplasia comprising determining the sequence of parts of a p53 gene, analyzing the nucleotide sequence for mutations, classifying patients depending on whether or not the neoplasia had a p53 mutation or not and providing a prognosis of the neoplasia depending on whether the neoplasia exhibited a p53 mutation or not.

Thorlacius et al teaches that p53 mutations are associated with a poor prognosis in patients with breast cancer (see abstract). Thorlacius et al teaches a method which comprises DNA sequencing of exons 5, 7 and 8 (page 1638, 1st column) and teaches that exons 5, 7 and 8 contain conserved regions of the p53 gene (page 1637, bridging paragraph between 1st and 2nd column). Thus, Thorlacius et al teaches a method which is the same as that claimed.

14. Claims 1, 2 and 4-7 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hedrum et al (cited in the IDS and in previous Office Actions) in view of Elledge et al (supra) and further in view of Callahan.

Claims 1, 2 and 4-7 are drawn to methods of prognosticating development of neoplasia and obtaining guidance for treatment of a neoplasia comprising the steps of determining the nucleotide sequence of a part of a p53 gene encoding a biologically functional domain; analyzing the nucleotide sequence for the presence of mutations; classifying the neoplasia in to different groups depending on the presence of a p53 mutation and whether or not the patient is node positive; and prognosticating the development of a neoplasia and providing guidance based on the classification results. The claimed methods do not delineate the relationship between any of the classification groups and a prognosis or guidance to be obtained (or provided).

Claim 14 is a method comprising the same steps as the method of claim 1 but is drawn to a method for prognostication of the development of neoplasia in a human patient having neoplasia.

The claimed methods are obvious over the prior art as a whole because it is well known that, at least in breast cancer, that the presence of p53 mutations indicates a poor prognosis for a patient with breast cancer, and that having a node positive status indicates a poor prognosis. Hedrum et al teaches a method of analyzing breast tumor samples for p53 mutations in exons 4-9 which encompass regions which are evolutionarily conserved and encompass a DNA binding domain (exon 7). The methods used are direct sequencing methods (page 118, 3rd column - page 119, 1st column; and page 123, 3rd column). Hedrum et al also teaches that direct sequencing methods are the most informative of methods for determining p53 mutations. Hedrum et al also

suggests that p53 mutations can provide prognostic information (page 118, 3rd column). Hedrum et al does not analyze a large population of samples and therefore does not provide a prognosis for patients. However, Elledge et al teaches that, in breast cancer, the presence of p53 mutations are clearly associated with a poor prognosis (see for example, page 98, 1st column). Both Hedrum et al and Elledge et al teach mutations which are mutations resulting in an amino acid substitution and Elledge et al also teaches deletion mutations which result in a frame shift and truncation. Elledge et al does not teach using nodal status as a second classification parameter. However, Callahan et al provides teachings to demonstrate that lymph node-positive patients with p53 positive tumors have a decreased overall survival. Thus, Callahan et al teaches that nodal status is useful second parameter for the prognosis of breast cancer.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have combined the teachings of Hedrum et al, Elledge et al and Callahan et al to have made the claimed methods of prognostication of neoplasia that are based on detecting p53 mutations and on determining the nodal status of a patient.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Anne Holleran, Ph.D. whose telephone number is (703) 308-8892. Examiner Holleran can normally be reached Monday through Friday, 9:00 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D. can be reached at (703) 308-3995.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist at telephone number (703) 308-0196.

ALH

Anne L. Holleran
Patent Examiner
February 18, 2001

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